BREAST CANCER SUMMARY

INTRODUCTION

More than 3,700 Wisconsin women were diagnosed with breast cancer and 854 women died from breast cancer in 1998. Detection and treatment of breast cancer require a high level of informed participation from the patient, in addition to a high degree of expert medical skill and efficient allocation of health care resources. This paper summarizes information about breast [A]cancer incidence, risk factors, prevention, mortality, and current research. This paper is a condensed source of general information. Further reading of referenced materials and discussion of individual questions with medical experts are encouraged.

WHO GETS BREAST CANCER?

General Incidence. Breast cancer is the most common cancer occurring among women in the United States. In Wisconsin, breast cancer accounts for approximately 33 percent of all female cancer cases. In 1998 (the latest year for which information was published), there were 4,372 new cases of ***pre-invasive and invasive*** breast cancer reported to the Wisconsin Cancer Reporting System (WCRS). Seventy-two percent of these cases were diagnosed in the earlier stages (in situ or local), 26 percent were diagnosed in more advanced stages (direct extension, regional, or distant), and 2 percent were reported as unknown in stage. The 1998 Wisconsin age-adjusted incidence rate for all invasive breast cancers was 111 per 100,000 female population (1).[A]

[A] Incidence numbers (newly diagnosed cases) are based on cases reported to the Wisconsin Cancer Reporting System as diagnosed in 1998. Incidence rates are per 100,000 residents, age-adjusted to the 1970 U.S. population. To calculate age-adjusted rates, age-specific rates are first determined, then weighted by multiplying each age-specific rate by the proportion of the 1970 U.S. standard population in that age group. The age-adjusted rate is the sum of the weighted age-specific rates.

Demographics

Age. The incidence of breast cancer increases with age, rising sharply after age 40. Nearly 80 percent of breast cancers in the United States occur among women 50 years of age and older; in 1998, 80 percent of invasive breast cancers in Wisconsin occurred among women 50 years of age and older (1). At age 50, a woman's chance of ever developing breast cancer is about 1 in 50; and by age 60, her chance is closer to 1 in 24 (2).

Race. According to the National Cancer Institute, national statistics for 1997 indicated that white women were more likely to develop invasive breast cancer (118 cases per 100,000 female population) than African-American women (103 cases per 100,000 population). However, African-American women were more likely to die of breast cancer (31 deaths per 100,000 population) than white women (23 deaths per 100,000 population) (3).

The North American Association of Central Cancer Registries (NAACCR) publishes incidence and mortality cancer data by race and sex. For the years 1993 to 1997, the NAACCR report showed that Wisconsin parallels the national pattern. There was a higher incidence rate for Wisconsin ***invasive*** breast cancer among white women (108 per 100,000) than African-American women (89 per 100,000), but there was a higher mortality rate among African-American women (27 per 100,000) than white women (24 per 100,000) (4).

Sex. Men can develop breast cancer, although the incidence is very low. From the 4,418 breast cancer cases reported to the WCRS in 1998, only 46 (1 percent) occurred among males. Breast cancer accounted for only 0.4 percent of total male cancer cases (1).

HOW HAS THE OCCURRENCE OF BREAST CANCER CHANGED OVER TIME?

Stage of Diagnosis. Breast cancer is detected earlier today than ever before, largely due to increased use of mammography. In 1985, only 4 percent of breast cancer cases in Wisconsin were diagnosed at the earliest pre-invasive stage (in situ). During the following decade, the diagnosis of earliest stage breast cancer increased dramatically, accounting for 15 percent of breast cancers diagnosed in 1998. This increase is attributed to increased mammography use (5). Correspondingly, diagnosis at the most advanced stage of breast cancer decreased from 7 percent in 1985 to 3 percent in 1998 (1).

Incidence Trends. The incidence for all stages (pre-invasive and invasive) of reported breast cancer has slowly increased over the last 15 years in Wisconsin, as well as nationally and internationally (6). The 1985 age-adjusted rate for Wisconsin was 92 cases per 100,000 population; the 1990 rate was 108 per 100,000; the 1998 rate was 132 per 100,000 (1). This general rise has been attributed to several factors, including more complete reporting, earlier detection of breast cancer, and the general aging of the population.

The rate of invasive breast cancer in the United States has stabilized at approximately 110 per 100,000 during the recent period 1990-1996 (7). The rate of invasive breast cancer in Wisconsin has remained at approximately 106 cases per 100,000 population during the recent 1990-1996 period, but increased to 111 in 1998 (1).

WHAT ARE THE RISK FACTORS FOR BREAST CANCER?

A number of variables, or personal characteristics, may predict a potential for breast cancer. Breast cancer risk means the possibility of developing breast cancer. The American Cancer Society (7) suggests women assess their risks relative to the following known risk factors:

Increasing age. Approximately 77 percent of women with new diagnoses of breast cancer are over age 50. Breast cancer, like most other cancers, is age-related; incidence rises with increasing age.

Family history of breast cancer. Breast cancer in a first-degree relative (mother, sister, or daughter) is associated with the highest risk, but any breast cancer in the family should be considered a factor for increased risk.

Genetic risk factors. Approximately 10 percent of breast cancer cases are due to heredity. Mutations of the BRCAI or BRCA2 genes have been linked with 40-50% percent of all hereditary breast cancers. Especially for women with breast cancer in their families, tests for this genetic susceptibility are available.

Personal history of benign or cancerous breast disease. Women with breast cancer in one breast have a risk three to four times greater than the general population of developing cancer in the other breast. Women with benign breast disease (atypical hyperplasia) have a breast cancer risk four to five times that of the general population.

Hormonal history. Early age at menarche (before 12 years), late age at menopause (after 50 years), late age at first birth, and few or no pregnancies all increase the risk of breast cancer. Medical research suggests that these conditions result in longer lifetime exposure to estrogen, which promotes cell division in breast tissue and may result in mutations.

Hormone replacement therapy (HRT). The majority of recent studies indicate that hormone replacement therapy with estrogen, as well as with combined estrogen and progestin, increase the risk of breast cancer. Long-term HRT (5 -10 years) may increase the risk by 10 - 20 percent, and the risk increases proportionately to the duration of use (8,9,10).

Obesity and high fat diets. Being overweight has been implicated as a risk factor for breast cancer. Large national studies have shown that obese women have somewhat higher incidence and mortality rates from breast cancer (11,12). A study from Harvard University followed 95,000 women for 16 years and determined that obesity after age 18 contributed to breast cancer diagnosed years later in post-menopausal women. Breast cancer risk was found to be 40 percent greater for women who had gained 44-55 pounds after age 18, than for women who had only a five-pound fluctuation during adulthood (13).

Alcohol. Reported by the American Cancer Society, a review of over 50 investigations found that consumption of alcohol increased breast cancer risk. Women who consumed approximately two drinks daily had increased their breast cancer risk by 25 percent (7).

The National Cancer Institute (NCI) recommends that women at higher risk seek medical advice before age 40. Higher risk is generally defined by NCI as one or more risk factors related to family history of breast cancer, genetic predisposition, or late age (30 or older) for first birth (14).

WHAT ARE THE MORTALITY AND SURVIVAL FIGURES FOR BREAST CANCER?

Recent mortality decline. Female breast cancer mortality has slowly declined both in Wisconsin and nationally in recent years. From 1980 to 1990 the Wisconsin mortality rate was relatively constant at 29 deaths per 100,000 women; by 1998, the rate had dropped to 22 deaths per 100,000 (1).[B] Since 1990, United States female breast cancer mortality has declined on average of 1.8% per year (7). This improvement is attributed to earlier screening and detection, as well as improved treatment of breast cancer.

Mortality perspective. Breast cancer mortality should be kept in perspective with two other leading causes of death among women. Since 1987 lung cancer has surpassed breast cancer in causing deaths, attributed to the increase in smoking among women. Heart disease is still the greatest threat to older women and causes four times the number of deaths as breast cancer in women over the age of 55.

Survival by Stage of Diagnosis

Stage at diagnosis. Generally, the stage at which breast cancer is diagnosed is critical because survival rates increase proportionately with earlier detection. The five-year national survival rate is 96 percent when breast cancer is diagnosed at a local stage (confined to the breast), 77 percent when diagnosed at a regional stage (spread to surrounding tissue), and 21 percent when diagnosed at a distant stage (cancer has metastasized) (7).

Early detection increases survival. The average number of months until death decreases as breast cancer is diagnosed at more advanced stages. For all 1998 deaths in Wisconsin due to breast cancer, the average number of months until death for breast cancer diagnosed at the local stage was 81 months; the average number of months until death for breast cancer cases diagnosed at the distant stage was 25 months (1).

HOW CAN BREAST CANCER BE PREVENTED OR CONTROLLED?

The best strategy to prevent or control cancer is to reduce modifiable risk factors by making healthy lifestyle choices, and follow the leading cancer organizations' guidelines for early detection.

[B] Deaths are from Bureau of Health Information files of resident death certificates, reflecting deaths that occurred in the years mentioned. Mortality rates are per 100,000 residents, age-adjusted to the 1970 U.S. population.To calculate age-adjusted rates, age-specific rates are first determined, then weighted by multiplying each age-specific rate by the proportion of the 1970 U.S. standard population in that age group. The age-adjusted rate is the sum of the weighted age-specific rates.

Early Detection

Recommendations for screening. The most recent guidelines, issued in March 1997 by the National Cancer Institute, recommend mammograms every 1 or 2 years for asymptomatic women 40 years and older. The American Cancer Society recommends more frequent annual mammograms for women age 40 and older. Women younger than 40 with known risk factors should have annual mammograms, or regularly scheduled mammograms based on the extent of estimated risk determined jointly by patient and physician.

Financial coverage. Medicare provides insurance coverage for annual mammograms for all eligible women. In Wisconsin, the National Breast Cancer Early Detection Program, sponsored by the Centers for Disease Control and Prevention (CDC), supports the Wisconsin Women's Cancer Control Program in the Department of Health and Family Services, which offers free screening to low-income women (annual household income at or below 200% of the Federal Poverty Guidelines) who are age 50 or older and who are uninsured or underinsured. The program also targets women living in rural areas, and black, Asian, Hispanic, and Native American women (15).

Lives saved by mammograms. According to the American Cancer Society, mammography is highly accurate and detects about 90 percent of breast cancers in women without symptoms, and is more accurate in postmenopausal women compared with pre-menopausal women (7). Improvement in mammogram screening was reported by the Behavioral Risk Factor Surveillance System. An average increase of 30 percent was reported from 1989 to 1995 in the use of mammograms among women age 40 and older. This analysis was based on data from 39 states, including Wisconsin, that participate in the CDC National Breast Cancer Early Detection Program (15). According to data from the 1997 Behavioral Risk Factor Surveillance System, 84 percent of U.S. women (40 years and older) reported ever having had a mammogram, and 83 percent of Wisconsin women reported ever having had a mammogram (7).

Clinical breast examinations. In addition to regular mammograms, breast examinations by trained medical professionals are important during annual physical examinations. All cancer organizations also recommend that women conduct monthly breast self-examinations.

Monthly self-examinations. Many women find breast irregularities that prompt early medical examination and treatment. A woman who finds a mass or abnormality should be seen promptly for appropriate clinical evaluation.

Early detection leads to breast conservation treatment. Although 80 percent of breast biopsies are proven benign, a physician must evaluate any lump (17). Since 1992, the National Cancer Institute has recommended breast conservation therapy, or lumpectomy, often with radiation, for early-stage breast cancer. Long-term studies have shown that breast conservation therapy is preferable to mastectomy for cancer diagnosed at an early stage (18).

Lifestyle Choices - Diet and Exercise

Eat fruits and vegetables. Dietary recommendations for the prevention of all types of cancer have emphasized the value of consuming a variety of fruits and vegetables. Since 1982 the National Research Council has made recommendations for the dietary prevention of cancer (19). The American Cancer Society, the National Academy of Sciences, and the National Cancer Institute also recommend a diet high in fruits and vegetables, particularly the cruciferous plants: broccoli, cabbage, cauliflower, and Brussels sprouts (20,21). Recent research also indicates benefits from cooked tomatoes, as a source of the chemical lycopene, (22) and broccoli sprouts, for an intensified source of anti-carcinogenic compounds (23). Researchers have recently estimated that plant-based diets could prevent 20 percent to 50 percent of all cancer cases (21).

Reduce dietary fat and avoid obesity. In general, research indicates that diets high in fat may increase the risk of breast cancer. This finding is largely based on differences in incidence rates between countries that have different levels of dietary fat intake (24). The prudent choice would be to limit both saturated fats from animal sources and trans-fatty acids from margarine and solid vegetable fats. Studies of obesity and breast cancer risk indicate obesity after menopause increases the risk of breast cancer and, given the high percentage of women who are obese in the U.S., weight control has become an important preventive measure (7).

Limit alcohol consumption. Moderate and heavy alcohol consumption is consistently associated with an increased risk of breast cancer (7, 25, 26). The American Cancer Society recommends a limit of one drink per day for those women who drink alcoholic beverages (27). An analysis of several studies concluded that alcohol consumption is associated with a linear increase in breast cancer, and that reducing alcohol as a preventive measure is a useful strategy for regular consumers of alcohol (28).

Exercise regularly. Physical exercise has been associated with lower incidence of breast cancer in a number of studies. A review of the research in a 1997 scientific workshop concluded that physical activity is inversely related to breast cancer (29,30,31). A 13-year study of approximately 25,600 women in Norway found that subjects who exercised regularly had a lower incidence of breast cancer than more sedentary women (32).

Tamoxifen - Breast Cancer Control and Prevention

The drug tamoxifen has been used for the treatment of some breast cancers. Recently large studies have demonstrated that tamoxifen can also be used to reduce the risk of breast cancer in women with known risk factors or with a history of breast cancer. High-risk groups receiving tamoxifen had a 49 percent reduction in breast cancer incidence compared to the control groups. However, side effects included an increased risk of endometrial cancer, and should be taken into consideration. A woman with an increased risk of breast cancer may discuss tamoxifen as a preventive measure with her physician (33).

WHERE TO FIND MORE INFORMATION

Web sites/numbers for general cancer topics, including breast cancer

National Cancer Institute Cancer Information Service Telephone: 1-800-4-CANCER
National Cancer Institute Cancer Net Website: http://cancernet.nci.nih.gov

American Cancer Society Telephone: 1-800-ACS-2345
Website: http://www.cancer.org

Centers for Disease Control and Prevention
National Center for Chronic Disease and Health Promotion
http://www.cdc.gov/cdp/index.htm

Cancer News on the Net
http://www.cancernews.com

Harvard Center for Cancer Prevention
http://www.hsph.harvard.edu/cancer/

Mayo Clinic Cancer Information (click on "Diseases and Conditions A-Z")
http://www.mayoclinic.com

Johns Hopkins Oncology Center
http://www.hopkinskimmelcancercenter.org

University of Pennsylvania Cancer Center- Oncolink
http://cancer.med.upenn.edu

Wisconsin Cancer Reporting System
http://www.dhfs.state.wi.us/wcrs/index.htm

University of Wisconsin Comprehensive Cancer Center
http://www.cancer.wisc.edu

MEDLINE - National Library of Medicine- Cancer
http://www.nlm.nih.gov/medlineplus/cancers.html

Department of Health and Human Services
National Women's Health Information Center
http://www.4woman.gov

Wisconsin Women's Cancer Control Program
Division of Public Health
Wisconsin Department of Health and Family Services
Telephone: (608) 266-8311

Web sites for breast cancer

National Alliance of Breast Cancer Organizations (NABCO)
http://www.nabco.org

Breast Cancer Network Newsletter
http://www.breastcancer.net

Centers for Disease Control and Prevention
National Breast and Cervical Cancer Early Detection Program
http://www.cdc.gov/cancer/nbccedp

National Breast Cancer Coalition
http://www.natlbcc.org

Susan G. Komen Breast Cancer Foundation Cancer Information
http://www.komen.org/bci/

Johns Hopkins Breast Center
http://www.med.jhu.edu/breastcenter

DEFINITIONS

Cancer – A group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death.

Cause - Cancer is caused by both external (chemicals, radiation, and viruses) and internal (hormones, immune conditions, and inherited mutations) factors. Causal factors may act together or in sequence to initiate or promote cancer. Ten or more years may pass between exposures and detectable cancer.

Risk factor – Something that increases a person's chance of developing a disease. Having a risk factor means a person has a greater chance of developing a disease than a person without the risk factor, but it does not predict with any certainty those who will develop a disease.

Cancer screening – Checking for changes in tissues, cells or fluids that may indicate the possibility of cancer when there are no symptoms. Regular screening exams can result in the detection of cancers at earlier stages, when treatment is more likely to be successful.

Cancer diagnosis – The detection of cancer based on symptoms or screening tests that confirm the presence of cancer cells. Diagnoses are based on the cancer site of origin; for example, a cancer originating in breast tissue is diagnosed as breast cancer, even if it has spread to other parts of the body.

Stage of disease at diagnosis – The stage of disease at diagnosis refers to the extent of the spread of disease at the time of diagnosis. The staging classification used in this report is the National Cancer Institute's Summary Staging Guide for Cancer: Surveillance Epidemiology and End Results Reporting. The summary stages are defined as follows:

> In Situ – A tumor that fulfills the microscopic criteria for cancer, but does not invade the surrounding tissues. This paper does not include in situ cases, but reports only invasive cancers. Most cancer publications exclude in situ cases, except for in situ bladder cancer.
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> Local – A malignant tumor that is confined to the organ of origin with no evidence of spreading to other parts of the body.
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> Regional – A malignant tumor that has spread beyond the limits of the organ of origin into adjacent organs or tissues by direct extension, or through regional lymph nodes, but appears to have spread no further.
>
> Distant – A malignant tumor that has spread to parts of the body remote from the organ of origin.

Rate – The number of events occurring in a specific population during a given period of time. Rates in this report are expressed per 100,000 population.

Cases – The incidence of a reportable primary site of origin for cancer. A cancer patient may be diagnosed with more than one primary cancer. The number of cases in this report refers to the number of primary cancers, not the number of cancer patients.

Incidence rate – The number of new cancer cases of a specific site occurring in a specified population during a year, expressed as the number of cancers per 100,000 population. It should be noted that the numerator can include multiple cancer sites occurring in one individual and, except for in situ bladder cancer, excludes in situ cases. All incidence rates in this report are standardized to the 1970 U.S. population.

Mortality rate – The number of deaths with cancer given as the underlying cause of death occurring in a specific population during a year, expressed as the number of deaths due to cancer per 100,000 population. All mortality rates in this report are standardized to the 1970 U.S. population.

Age-adjusted rate – The incidence and morality per 100,000 population expected for Wisconsin if the state's age distribution were the same as that of the standard population. For incidence and mortality in this report, the standard population used was the 1970 U.S. population. Age-adjusted rates allow comparisons between different population groups by controlling the effects of age differences between populations.

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References

1. Wisconsin Cancer Reporting System. *Wisconsin Cancer Incidence and Mortality, 1998*. Cancer Reporting System, Bureau of Health Information, Division of Health Care Financing, Wisconsin Department of Health and Family Services, 2000.

2. Mayo Foundation for Medical Education and Research. Breast Cancer. New perspectives can replace unrealistic fears. *Medical Essay Supplement, Mayo Clinic Health Letter,* 1994.

3. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Clegg L, Edwards BK (eds). *SEER Cancer Statistics Review, 1973-1997.* National Cancer Institute, 2000.

4. Chen VW, Howe HL, Wu XC, Hotes JL, Correa CN (eds). *Cancer in North America, 1993-1997. Volumes I and II: Incidence and Mortality*. North American Association of Central Cancer Registries, 2000.

5. Bush DS, Remington PL, Reeves M, et al. In situ breast cancer correlates with mammography use, Wisconsin: 1980-1992. *Wisconsin Medical Journal* 93(9): 483-484, 1994.

6. Muir C, Warehouse J, Powell J, Whelan S. *Cancer in Five Continents*. Vol V. International Agency for Research on Cancer, 1987.

7. American Cancer Society. *Breast Cancer Facts & Figures 1999-2000*. American Cancer Society, 1999.

8. Beral V, Bull D, Doll R, et al. Breast cancer and hormone replacement therapy: collaborative reanalyzes of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *The Lancet* 350:1047-59, 1997.

9. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in post-menopausal women. *The New England Journal of Medicine* 332:1589-93, 1995.

10. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of Hormone Replacement Therapy on Breast Cancer Risk: Estrogen Verses Estrogen Plus Progestin. *Journal of the National Cancer Institute* 92 (4) 328-332, 2000.

11. Lew EA, Garfinkel L. Variations in mortality by weight among 750,000 men and women. *Journal of Chronic Disease* 32: 563-76, 1979.

12. Ziegler RG, Hoover RN, Nomura AM, et al. Relative weight, weight change, height, and breast cancer risk in Asian-American women. *Journal of the National Cancer Institute* 88:650-60, 1996.

13. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. *Journal of the American Medical Association* 278:1407-1411, 1997.

14. National Cancer Institute. Cancer Facts. *Cancer Research. Because Lives Depend on It*. National Cancer Institute, National Institutes of Health, 1997.

15. Johnson GD, Garrett LA, and Benzie RM. The Wisconsin Women's Cancer Control Program: 1993-1995. *Wisconsin Medical Journal 94(10): 553-554, 1995*.

16. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report*. 46(40): 937-941, 1997.

17. National Alliance of Breast Cancer Organizations. *NABCO Fact Sheet, Facts About Breast Cancer in the USA, 1997*.

18. Fisher B, Anderson S, Redmond CK, Wolmark N, et al. Reanalyses and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *New England Journal of Medicine* 333:1456-1461, 1995.

19. Fahey JW, Zhang Y, Talalay P. *Proceedings from the National Academy of Sciences, USA 94*: 10367-10372.

20. World Cancer Research Fund and American Institute for Cancer Research. *Food, Nutrition, and the Prevention of Cancer: A Global Perspective*. World Cancer Research Fund and American Institute for Cancer Research, Washington, DC. 1997.

21. American Cancer Society Advisory Committee on Diet, Nutrition, and Cancer Prevention. The Importance of Nutrition in Cancer Prevention, *A Cancer Journal for Clinicians* 46; 325-341, 1996.

22. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: a review. *Journal of the American Dietetic Association* 96; (10): 1027-1039, 1996.

23. Nestle M. Broccoli sprouts as inducers of carinogen-detoxing enzyme systems: Clinical, dietary, and policy implications. *Proceedings from the National Academy of Sciences* 94:11149-11151, 1997.

24. Prentice RL, Sheppard L. Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. *Cancer Causes Control* 1: 81-97, 1990.

25. Longnecker MP. Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. *Cancer Causes Control* 86: 589-599, 1994.

26. Bowen, et al. Alcohol intake linked to breast cancer, *International Journal of Epidemiology* 26: 915-923, 1997.

27. American Cancer Society. *What are the Risk Factors for Breast Cancer?* Breast Cancer Resource Center, American Cancer Society, *2000*. Online: http://www.cancer.org

28. Smith-Warner S, Spiegelman D,Shiaw-Shyuan Y, et al. *Alcohol and breast cancer in women: a pooled analysis of cohort studies,* JAMA: 279:535-540,1998.

29. Friendenreich CM, Thune I, Brinton LA, Albanes D. *Epidemiologic issues related to the associations between physical activity and breast cancer*. Cancer; 83(3Suppl):600-610, 1998.

30. Albanes D, Blair AA, Taylor PR. Physical activity and risk of breast cancer in the NHANES I population, *American Journal of Public Health* 79:744-50, 1989.

31. Colditz G. *The Harvard Center for Cancer Prevention Annual Report*. December 1997.

32. Thune I, Brenn T, Lund E, and Gaard M. Physical activity and the risk of breast cancer, *The New England Journal of Medicine* 336(18): 1269-75, 1997.

33. Fisher B, Costantino JP. Wickerham DL, Remond CK, et al. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project. *Journal of the National Cancer Institute*; 90:1371-1388, 1998.